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Article

Evaluation and Treatment of Nuclear Casualties: Part III—Management of Combined Injuries

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This is the last part in a series of three articles on the evaluation and treatment of nuclear casualies.

The instability of world politics and the proliferation of nuclear weapons have increased the likelihood that health professionals will deal with situations of mass casualties. Recent estimates suggest that 32 countries will have a nuclear capability by the year 2000.[1] Any subsequent casualties will suffer radiation injuries alone or in combination with blast and thermal injuries. In the event of an accident, the physician's primary task is to assess the severity of the radiation or combined injury. Significant and even potentially lethal doses have been received by persons who have been unknowingly exposed to a radiation source. Unfortunately, in some cases, improper diagnoses delayed the onset of treatment or even permitted the exposure to continue. A far different picture emerges when considering the radiation casualties resulting from the detonation of a nuclear weapon. In this situation, health care personnel will face the ultimate challenge. Casualties will be many, and resources will undoubtedly be inadequate. Of prime importance will be the salvaging of those victims who require only minimal initial treatment and resources. Further complicating this situation will be the fact that most of the radiation casualties will have additional injuries from the blast and thermal effects of the detonation itself.

Injuries, benign when alone, become lethal when combined with relatively small doses of whole-body irradiation. This has produced a unique set of problems for the military physician. Unfortunately there are very few clinically relevant studies for guidance. The decrease in survival with combined injuries has been observed for many years in automobile accident victims. Blunt or sharp trauma by itself may cause minimal morbidity, but the addition of a small burn will often result in death. Radiation injury also greatly magnifies the problem. Estimates of the incidence of combined injuries have been predicted, based on the Hiroschima and Nagasaki experiences as follows:[2]

Burn and wound and radiation injury	20%
Burn and radiation	40%
Mechanical and radiation injury	5%
Others	35%

Since there is no immediate life-threatening hazard for the person who has the potential for surviving a radiation injury, the physician should initially be concerned with primary resuscitation. Only then should time be spent in assessing the possibility of radiation injury. In either the field or hospital setting, health workers should not delay handling victims of a radiation accident or nuclear weapon detonation. If health workers wear surgical attire and use dosimetry equipment, they can handle these patients in an appropriate manner.

Regardless of the type of exposure or contamination, the physician's initial response to a patient with radiation injury is the life-saving treatment of nonradiation injuries. The first actions must be the standard emergency medical procedures: ensure that the patient has an open airway and is ventilated, that adequate perfusion is maintained, and that life-threatening hemorrhage has been stopped. Once the patient is stabilized, other actions can be taken. It is essential to reaffirm that potentially survivable radiation injuries are not acutely life threatening and that traumatic and burn injuries will be more important. Once the patient is stabilized, decontamination may be initiated. When feasible, decontamination may be performed simultaneously with treatment.

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The biological effects induced by combined injuries will markedly increase the casualty burden and will significantly decrease the patient's ability to survive and recover. Patients with combined injuries at Hiroshima and Nagasaki developed significant complications at two or three weeks after exposure to levels that produce hematopoietic depression. Open wounds of many patients stopped healing, lacked granulation tissue, and hemorrhaged. These patients lost weight, and many died of sepsis. While support systems for the care of the critically ill patient or trauma patient have increased the patients chance for survival, it will be difficult, if not impossible, to predict at the time of triage which patients with traumatic injuries will develop radiation sickness.[9] The prodromal symptoms, which are useful in assessing the radiation exposure, may be unreliable when occurring in association with conventional trauma.

General Considerations

Messerschmidt[29] summarized much of the Warsaw Pact data by stating that an open wound markedly increases the chances of infection, and he recommends immediate closure of the wound, a therapeutic alternative inconsistent with current battlefield surgery.[6] Open skin wounds were induced on the backs of mice before and after 510 R whole-body irradiation. Average healing time increased from 16 to 24 days when the wounds were made within two hours of irradiation whereas wounds made one to four days before irradiation increased the healing time from 16 to 18 days. This and other experiments have shown the significant effect of the presence and timing of irradiation exercises on all the components of wound healing.

Ledney et al,[7] showed that skin-wound trauma of a 4% surface area before irradiation raised the LD50/30 by 20% and this lesion after radiation did not decrease the LD50/30. Similar results were reported by Stromberg,[8] in which case a 3-cm-diameter skin wound was inflicted before and after photon irradiation of 875 R. It has also been shown that aseptic resection of a 10-cm section of canine ileum after 200-300 R of whole-body irradiation does not alter mortality.[9] Messerschmidt conducted extensive studies in mice on the impact of open and closed wounds, splenectomy, laparotomy, and soft tissue injury in addition to 510 R whole-body irradiation.[10] As in the previously described studies, mortality increased when the wound was inflicted after irradiation and decreased if the wound was inflicted before irradiation. This increased survival may be due to increased myelopoiesis when the trauma occurs before irradiation.[11]

Messerschmidt[12] applied a contact burn to mice before and after 510 R whole-body irradiation. The radiation exposure had a 10% mortality and the contact burn had a 30% mortality. The combination of these injuries resulted in an increase in mortality to 90%. Brooks et al,[13] showed that as little as 25 R increased the mortality in dogs with a burn of 20% body surface area; the combination of 100 R irradiation with a burn of 20% body surface area increased mortality from 12% to 75%.

The impact of whole-body irradiation on the healing of a bone fracture is also important to the military physician. Zemljanoj[15] followed callus formation radiographically and histologically in rabbits from which a piece of subperiostial radius had been removed two hours after receiving 800 R (LD20/30) irradiation. The control-group rabbits were completely healed by day 32 whereas the irradiated animals did not show complete healing until 60 days postirradiation.

Early closure of wounds is desired in combined injuries of soft tissue, but it is not always possible, any primary closure is proscribed in battlefield casualties.[6] Since an open wound is exposed to colonization and possible systemic sepsis; conventional soft-tissue wounds in the patient with combined injuries may significantly enhance the development of sepsis. The immunoparalysis caused by combined injuries is much more severe than the trauma from a single injury. The bone marrow stem cells are very sensitive to radiation and may require more than a month to recover; during this time, the patient's immune system is dangerously depressed. Ionizing radiation compromises the patient with respect to its natural defenses against infectious disease, endogenous gut-derived bacteria, and associated toxins. An early phase of nonspecific cell-mediated resistance plays a vital role in the first line of defense against bacterial disease.

As described in Part II of this manuscript the major part of early resistance to infection is determined by the ability of both the circulating and the tissue granuloctyes and macrophages to kill invading micro-organisms and to release a variety of immunostimulatory and hematopoietic factors. Macrophages are relatively radioresistant and survive for long periods of time in *in situ*. It follows that their function during periods of leukopenia after radiation injury is important. Galelli and associates,[16,17] using a murine model, recently demonstrated the primary role of radioresistant cells in nonspecific resistance to infection.

Injuries to the abdomen also present many potentially significant problems in the irradiated patient.

Blast overpressure, blunt trauma, and penetrating wounds are all significant causes of abdominal injury. Most of the research in this area has been performed by Soviet investigators. In one of those studies, partial resection of the ileum or stomach in rabbits at varying times postirradiation, produced the least mortality when performed immediately after irradiation or during the latent period. Mortality increased when surgery was performed during the period of manifest illness.[16] In another study, dogs were irradiated with an exposure that was lethal in 7% of the animals.[17] An abdominal gunshot wound had a lethality of 12.5% with surgery. When the wound was inflicted and operated during the latent period of the radiation injury, the mortality was 47%, which increased to 63% when the wound occurred during the period of manifest illness.

As previously mentioned, combined injuries represent a spectrum of complicated problems in medicine and surgery. Many of these injuries may require treatment involving the administration of anesthetics, analgesics, or antibiotics-either singly or in combination. Few data are avilable to guide the military physician, such as the drug nomograms developed for renal failure patients. Significant alterations occur in the gastrointestinal tract postirradiation and many of the combined injury patients may receive anesthetics or they may be comatose. The possibility of altered drug metabolism seems to indicate that drugs should be administered parenterally. In addition, other changes occur postirradiation that may seriously alter the patient's response to drugs including: changes in permeability of the blood-brain barrier, changes in hepatic detoxification enzymes, and sensitization of the brain to drugs. The Soviet manual on *Medical Questions Concerning Radiation Protection* notes the increased toxicity and sensitivity of compromised patients to numerous drugs. For example it states: "the narcotic effects of barbiturates decrease in the hours after radiation injury. Yet a 95%-200% sedation dose may be decreased to 20%-45% postirradiation. Finally, attempts to achieve deep sedation results in serious complications that can be fatal." Davis and Strike exposed mice to a mixed neutron-gamma field.[19] They noted that the LD50 dose of some drugs significantly decreased by six days postirradiation. Toxicity was related to the radiation dose and the time postirradiation. The anticonvulsants mephenytoin, phenobarbital, and dephenylhydantoin were significantly more toxic, whereas several psychopharmacologic agents did not show an increase in toxicity until very high exposures (10 times the LD50/30).

Although all of the previous recommendations for treating radiation casualties still apply, the prognosis for almost all of the combined injuries is worse than for radiation injury alone. Combined injured patients will probably be significantly more susceptible to shock if the results observed in animals apply to humans.[20] A warm, quiet environment coupled with adequate but not excessive analgesia and maintenance of vascular volume should minimize circulatory collapse. The initial healing of burns, fractures, and wounds is not significantly altered if they occur within two days of the irradiation; but, subsequent healing will be significantly altered. In addition to profound immunoparalysis, the subsequent potential for hemorrhage postirradiation suggests that surgical interventions should be performed within hours or days of the radiation insult. The increased toxicity of some anesthetics and analgesics suggests that extreme caution should be exercised in the administration of these drugs, beginning at 24 hours postirradiation and continuing for 21 days.

The United States Army plans to field a radioprotective drug within five years. Stromberg and colleagues[21] demonstrated the efficacy of radioprotective compounds on combined injury. In rats,[22,23] the radioprotectants beta mercaptoethylamine (MEA), serotonin, or the phosphorothiate WR2721 were infused at 15 minutes before irradiation, skin wound, or combined injury. The radioprotectants alone did not alter healing of the wound, but the mortality in the combined injury decreased by 97% to 29% with serotonin, to 30% with MEA, and to 52% with WR2721. It is surprising that WR2721, the most effective radioprotectant for pure radiation injuries, should be less effective than the other agents in treating combined injury. Initial use of WR2721 in cancer patients has shown a disturbing level of toxicity. Clearly these studies need to be repeated in other species, with optimal schedules of drug dosage and newer preparations of radioprotectants.

Studies with animals indicate that antimicrobial therapy will be a significant approach to the management of combined injury. Donat et al,[22] demonstrated the importance of the infectious complications of combined injury by comparing wound healing and mortality in germ-free and conventional rats as previously described (II-5). Brooks et al,[13] noted a marked mortality in dogs exposed to a 20% contact burn and 100 R whole-body irradiation. The 75% mortality in the combined injury was reduced to 14% by daily administration of 900,000 units of procaine penicillin intramuscularly, beginning on the day after injury and continuing for 17 days. Baxter et al,[24] conducted similar studies in pigs to evaluate the efficacy of

streptomycin. The pigs were irradiated with 400 R whole-body irradiation in addition to a 10%-15% flash burn, with a resultant mortality of 90%. Approximately 25 mg/kg of streptomycin administered intramuscularly reduced mortality to 20%.

Based on the previously described infectious complications in radiation injuries and combined injuries, several approaches to the control of infection seem prudent. Isolation techniques may be useful, but are likely to be impractical because of the number of casualties. As a minimum, extreme effort should be made to prevent colonization of the patient by opportunistic pathogens. The use of non-absorbable broad-spectrum antibiotics and antifungal agents such as nystatin are warranted. Consideration should be given to selective decontamination of the gut with the use of agents like trimethoprim and sulfamethoxazole. A caveat must be given on the prophylactic use of trimethoprim-sulfamethaxazole (TMP-SMX). Despite early enthusiasm for this regimen, recent reports[25,26] have shown the development of TMP-SMX-resistant enterobacteriacea. These trends must be continually reviewed. Septic complications are often secondary to endogenous flora and will require broad-spectrum antibiotic coverage. If intra-abdominal sepsis occurs secondary to traumatic bowel perforation or surgery, then drug regimens effective against coliforms and anaerobes are indicated.[27] The prophylactic antibiotics should be continued in combined injuries (especially burns) until the neutrophils are above 1500 per cubic millimeter.[28] As previously described, non-specific immune enhancement has great potential (II-7). Specific vaccines or monoclonal antibodies for opportunistic pathogens or core glycolipid of Gram negative bacteria, when available, may be particularly useful in preventing the complications with these organisms. Clinical trails with approaches such as outlined above are warranted and military physicians must remain alert to evolving therapeutic strategies.

Debridement of all wounds must be meticulous, with the excision of all devitalized tissue to prevent any nidus for infection. Penetrating wounds of the small intestine can probably be resected and an anastomosis accomplished successfully if the surgery is done close to the time of irradiation. No data exist on how to manage injuries to the right or left colon. Eisman and Bond recommend primary repair to the right colon and exteriorization of the transverse and left colon.[29] In any burns and avulsion injuries, data from colleagues in France suggest that a biologic covering will very favorably increase survival. As long as the graft is placed shortly after the irradiation, it heals slowly but adequately. Any staged procedures or reconstructive surgery should be planned for after the resolution of the hematopoietic depression. Organ transplant surgeons probably have the greatest expertise to be shared, which would help provide guidelines for the management of a combined injury patient. These surgeons will have to be a primary resource until experimental studies can provide more adequate guidelines for therapy.

Until definitive data is available Scraiber and Korchanov recommend that the surgeon remember several important aspects about combined injuries.[30] The latent period is shortened compared to pure radiation injuries. The patient will suffer a reduction in non-specific resistence to infection in general, and to wound infection in particular. Granulocytopenia and thrombocytopenia are accelerated and more profound than in the pure radiation insult. Wound healing is markedly delayed and may profoundly alter therapy. Any significant blood loss will result in an early appearance of hypochromic anemia. Shock from any etiology (hemorrhage, septic) may be refractory to conventional therapy. The lethality from combined injuries is synergistic and the appearance of complications is accelerated.

On the integrated battlefield of the future, particularly in the NATO theater, chemical warfare agents may be added to the combined injuries already discussed. A definitive review of this added insult is beyond the scope of this review. Several salient points are nevertheless important. In pure radiation casualties resuscitation has a higher priority than decontamination. This is not true for a chemical casualty. The US Army Medical Research Institute of Chemical Defense recommends:

"Full decontamination: Exactly where and when full decontamination of contaminated casualties occurs may vary. It must be performed before full definitive care can be given, since the medical care providers can give only limited care wearing the protective ensemble."[30]

In an integrated battlefield scenario it will be prudent to decontaminate before providing definitive care. Preparation for surgery (removal of clothing and scrubbing) will remove 70-90% of the radiological contaminants.

Brigadier General T.J. Whelan, Jr. recently wrote a cogent review of "Surgical Lessons learned in the Care of the Wounded."[6] We emphatically support his recommendations for conventional trauma. An exhaustive review of the literature and data from our laboratory suggest some caution in several areas. The dictum of delayed primary closure for soft

tissue injuries has been learned the hard way in recent wars. The profound immuno-paralysis associated with combined injuries allows open wounds to provide a culture medium and portal of infection in addition to the gut as described in Part II of this review.[33] The use and timing of biological covering must be aggressively studied to provide simple guidelines to the combat surgeon. The use of prophylactic antibiotics before surgery has remained controversial.[34] We heartily support Dr. Whelan's recommendation for the use of broad spectrum antibiotics in any abdominal surgery.[6] Several European countries have adopted the prophylactic use of drugs like trimethoprim-sulfamethoxazole in all irradiated patients because endogenous gut flora may cause sepsis.[33,35] Sanford recommends meticulous debridement as well as systemic antibiotics for soft tissue injuries complicated by irradiation.[36]

Another area of controversy involves splenic injuries. Current NATO doctrine requires injuries of the spleen to be treated by splenectomy.[37] King noted the marked increase in infections postsplenectomy in children.[38] Pneumococcal infection was particularly increased leading to fulminant septicemia. The risk of postsplenectomy infection secondary to trauma is 50 times greater than in the normal population and much higher than in many hematologic disorders.[39,40] Recent reports have also shown an increase in sepsis secondary to Gram negative organisms.[42] In addition Scher has shown that splenectomy in rats impairs the ability to clear nonencapsulated bacteria (eg, *E coli*) from the bloodstream.[42] There has consequently been a trend to conservative management of splenic trauma.[41] What is not known, is how combined injury patients will behave post splenectomy. If this insult is like all other combined injury insults postsplenectomy sepsis will be exacerbated. In the future, the military surgeon will have to seriously consider methods to preserve the traumatized spleen.[43,44]

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